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CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES,
FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG,
MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT,
RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT,
TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent
(BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ,
TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK,
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nations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY,
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MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
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KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH,
CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU,
MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF,
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GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC,
SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA,
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For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: MODIFIED NATURETIC COMPOUNDS, CONJUGATES, AND USES THEREOF

(57) Abstract: Modified natriuretic compounds and conjugates thereof are disclosed in the present invention. In particular, conju-
gated forms of hBNP are provided that include at least one modifying moiety attached thereto. The modified natriuretic compound
conjugates retain activity for stimulating cGMP production, binding to NPR-A receptor, and in some embodiments an improved
half-life in circulation as compared to unmodified counterpart natriuretic compounds. Oral, parenteral, subcutaneous, and intra-
venous forms of the compounds and conjugates may be prepared as treatments and/or therapies for heart conditions particularly
congestive heart failure. Modifying moieties comprising oligomeric structures having a variety of lengths and configurations are
also disclosed. Analogs of the natriuretic compound are also disclosed, having an amino acid sequence that is other than the native
sequence.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/37996

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K38/22 A61K47/48 C07K14/58 C07K14/72 C08G65/32
C08G65/329 C08G65/333

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07K C08G

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, MEDLINE, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|
| X | US 5 342 940 A (KAI YOSHIYUKI ET AL) 30 August 1994 (1994-08-30) Example 24. | 1-13, 23-33, 40-61, 86-103, 105-126, 156-160 |
| X | WO 00/78302 A (EKWURIBE NNOCHIRI ;PROTEIN DELIVERY INC (US); RAJAGOPALAN JAYANTHI) 28 December 2000 (2000-12-28) Formula 2 at p. 9 and paragraph bridging pages 19 and 20. ----- -/-- | 1-13, 23-33, 40-61, 86-103, 105-126, 156-160 |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

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INTERNATIONAL SEARCH REPORT

I
 1al Application No
 PCT/US 03/37996

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| A | <p>CHANG T K ET AL: "Subtiligase: a tool for semisynthesis of proteins." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA. UNITED STATES 20 DEC 1994, vol. 91, no. 26, 20 December 1994 (1994-12-20), pages 12544-12548, XP002280083 ISSN: 0027-8424 Abstract; "Peptide Ligation" at p. 12545.</p> | <p>1-13, 23-33, 40-61, 86-103, 105-126, 156-160</p> |
| A | <p>US 6 162 902 A (SCARDINA JAN MARIAN ET AL) 19 December 2000 (2000-12-19)</p> <p>Seq. Id. No.: 4 and Figure 1-3</p> | <p>1-13, 23-33, 40-61, 86-103, 105-126, 156-160</p> |
| A | <p>EP 0 295 679 A (DAIICHI PURE CHEMICALS CO LTD ;MATSUO HISAYUKI (JP)) 21 December 1988 (1988-12-21) cited in the application</p> <p>Claim 1.</p> | <p>1-13, 23-33, 40-61, 86-103, 105-126, 156-160</p> |
| A | <p>CONDON: J. AM. OIL. CHEM. SOC., vol. 71, no. 7, 1994, pages 739-741, XP001181312</p> <p>Scheme 1.</p> | <p>1-13, 23-33, 40-61, 86-103, 105-126, 156-160</p> |
| P,X | <p>WO 02/098446 A (EKWURIBE NNOCHIRI N ;PRICE CHRISTOPHER H (US); ANSARI ASLAM M (US)) 12 December 2002 (2002-12-12) cited in the application</p> <p>Examples 52, 57, 59; Figures 1-10</p> | <p>1-13, 23-33, 40-61, 86-103, 105-126, 156-160</p> |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/37996

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 114-121
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 114-121 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-129, 156-160
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-11, 13, 23-33, 40-51, 86-103, 105-126, 156-160(all partially), 12
52-61 (completely)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

at Application No

PCT/US 03/37996

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| A | <p>CHANG T K ET AL: "Subtiligase: a tool for semisynthesis of proteins." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA. UNITED STATES 20 DEC 1994, vol. 91, no. 26, 20 December 1994 (1994-12-20), pages 12544-12548, XP002280083 ISSN: 0027-8424 Abstract; "Peptide Ligation" at p. 12545.</p> | <p>1-13, 23-33, 40-61, 86-103, 105-126, 156-160</p> |
| A | <p>US 6 162 902 A (SCARDINA JAN MARIAN ET AL) 19 December 2000 (2000-12-19)</p> <p>Seq. Id. No.: 4 and Figure 1-3</p> | <p>1-13, 23-33, 40-61, 86-103, 105-126, 156-160</p> |
| A | <p>EP 0 295 679 A (DAIICHI PURE CHEMICALS CO LTD ;MATSUO HISAYUKI (JP)) 21 December 1988 (1988-12-21) cited in the application</p> <p>Claim 1.</p> | <p>1-13, 23-33, 40-61, 86-103, 105-126, 156-160</p> |
| A | <p>CONDON: J. AM. OIL. CHEM. SOC., vol. 71, no. 7, 1994, pages 739-741, XP001181312</p> <p>Scheme 1.</p> | <p>1-13, 23-33, 40-61, 86-103, 105-126, 156-160</p> |
| P,X | <p>WO 02/098446 A (EKWURIBE NNOCHIRI N ;PRICE CHRISTOPHER H (US); ANSARI ASLAM M (US)) 12 December 2002 (2002-12-12) cited in the application</p> <p>Examples 52, 57, 59; Figures 1-10</p> | <p>1-13, 23-33, 40-61, 86-103, 105-126, 156-160</p> |

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 03/37996

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 114-121
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 114-121 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-129, 156-160
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-11, 13, 23-33, 40-51, 86-103, 105-126, 156-160(all partially), 12
52-61 (completely)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Continuation of Box I.1

Although claims 114-121 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 114-121

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Continuation of Box I.2

Claims Nos.: 1-129, 156-160

Present claims 1-127, 156-160 relate to an extremely large number of possible conjugates (claims 1-127, 156-160), namely conjugates comprising a natriuretic compound, a modifying moiety conjugation site and/or a modifying moiety; or to an extremely large number of possible natriuretic peptide analogues (claims 128-129), namely analogues comprising a modifying moiety conjugation site. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the natriuretic peptide analogues and the modifying moiety claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the conjugates comprising the natriuretic compounds explicitly mentioned at pages 10, 11, in the examples and in claims 12, 14, 34, 37, 130, 132, 134, 141, 176, 178 and 180 and the modifying moiety mentioned at pages 37-41, in the examples, table 1 and in claims 52, 62, 73, 161-175.

Present claims 1-11, 59-61, 70-72, 83-85, 100, 101, 105-108, 110, 156-160 relate to a compounds defined by reference to a desirable characteristic or property, namely retaining a certain percentage of cGMP stimulating activity (claims 1-11, 156 and 157); rendering the compound more lipophilic or hydrophilic or amphiphilic (claims 59-61, 70-72, 83-85, 100, 158, 159 and 160); a bond being hydrolysable or not hydrolysable (claims 101, 105-108 and 110). The claims cover all the compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited

number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the natriuretic compounds explicitly mentioned at pages 10, 11, in the examples and in claims 12, 14, 34, 37, 130, 132, 134, 141, 176, 178 and 180 and the modifying moiety mentioned at pages 37-41, in the examples, table 1 and in claims 52, 62, 73, 161-175.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: Claims 1-11, 13, 23-33, 40-51, 86-103, 105-126, 156-160 (all partially); 12, 52-61 (complete)

Natriuretic peptide conjugates according to the peptide of claim 12 and the polyethylene glycol of claim 52.

Invention 2-12: Claims 1-11, 13, 23-33, 40-51, 86-103, 105-126, 156-160 (all partially); 12, 14-22, 34-36, 37-39, 52-61, 62-72, 73-85 (all complete)

Each of the natriuretic peptide conjugates resulting from the combination of the peptides of claims 12, 14, 34 or 37 and dependent claims and the polyethylene glycols of claims 52, 62 or 73 and dependent claims, except those of invention 1.

Inventions 13-19: Claims 1-11, 13, 23-33, 40-51, 86-103, 105-126, 156-160 (all partially); 12, 14-22, 34-36, 37-39 (all complete)

Each of the natriuretic peptide conjugates resulting from the combination of the peptides of claims 12, 14, 34 or 37 and dependent claims and the polyethylene glycols of table 1 grouped according to their structure as follows:

Group i: BN-002, BN-002 SCALED UP, BN-003, BN-004, BN-011, BN-012, BN-024, BN-024 SCALED UP, BN-025.

Group ii: BN-007, BN-008, BN-010, BN-018, BN-019.

Group iii: BN-013, BN-014, BN-015, BN-016, BN-017.

Group iv: BN-022, BN-022 SCALED UP, BN-030.

Group v: BN-034, BN-038.

Group vi: BN-041, BN-042.

Group vii: BN-046.

Invention 20: Claim 127

Pro-polynatriuretic peptide conjugates according to claim 127.

Invention 21-28: Claims 130-155

Each of the natriuretic peptide analogues according to claims 130, 132, 134, 141, 147, 153, 154 or 155 and their dependent claims.

Invention 29-32: claims 161-175

Each of the polyethylene glycol derivatives of according to claims 161, 162, 163 (and 164), 165 (and 166) and method for their preparation.

Inventions 33-35: Claims 176-181

Each of the natriuretic peptide analogues of claims 176, 178 or 180 and their dependent claims.

INTERNATIONAL SEARCH REPORT

In International Application No
F... JS 03/37996

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